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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,050	PASTERNAK, GAVRIL W	
	Examiner	Art Unit	
	Jody L. Karol	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of applicant's Amendment/Remarks filed 11/13/2008. Claims 3-6 and 20-25 have been amended. Claims 1-2 and 10-19 remain withdrawn as directed to the nonelected invention. Thus, claims 1-25 are currently pending, and claims 3-9 and 20-25 are under consideration.

Priority

1. As noted in the 5/14/2008 office action, this Application is a 371 of PCT/US03/09766 International Filing Date: 3/27/2003, which claims priority to Provisional Application Nos. 60/367,793 and 60/416,414 filed on 3/27/2002 and 10/27/2002. In view of the Notification of Typographical Error in the Executed Declaration filed on 11/13/2008, the benefit of filing date of the earlier filed applications is granted.

WITHDRAWN REJECTIONS

1. In view of Applicant's amendment to Table 1, the objection to the specification is herein withdrawn.

2. In view of the Notification of Typographical Error in the Executed Declaration filed on 11/13/2008, the rejection of claims 3-5, 7-9, and 20-25 under 35 U.S.C. 102(b) as anticipated by Bolan et al. (*J. Pharm. Exp. Ther.*, 2002; 303: pgs 557-562) and the

rejection of claims 6 under 35 U.S.C. 103(a) as obvious over Bolan et al. are herein withdrawn.

3. In view of Applicant's amendment to claims 3-4 and 22-25, the rejection of claims 3-4, 7-9, and 22-25 as anticipated by Smith et al. (*J. of Pharm. And Exp. Therapeutics*, 1954; 108: pgs. 336-339) is herein withdrawn.

Response to Arguments

4. Applicant's arguments filed 11/13/2008 have been fully considered but they are not persuasive.

Applicant argues that Inturrisi teaches away from combination with Smith et al. as Inturrisi seeks to avoid the tolerance and physical dependence which are the consequences of chronic administration of morphine and morphine-like opioids. Applicant further argues that because Inturrisi attributes the opioid properties of racemic methadone are attributed to the L-isomer, one of ordinary skill in the art would not have been motivated to combine L-methadone with Smith without the risk of creating a greater dependence.

In response, it is respectfully submitted that that Inturrisi is solely used to demonstrate that L-methadone has increased opioid activities, and thus increased analgesic effects compared to D-methadone (see Figure 2 and column 3, lines 32-33). Since the claims are directed to a method of providing analgesia, it would be obvious to one of ordinary skill in the art to use the isomer with the increased analgesic activity, the

L-isomer. Furthermore, it is well settled patent law that optical isomers would have been expected to possess different therapeutic activities. Most biological systems are sensitive to optical isomerism, motivating the skilled artisan to expect one or another optical isomer to effect greater, or lesser physiological activity.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Applicant further argues that unexpected results over the prior art with regards to the synergistic combination of L-methadone with an additional opioid analgesic have been demonstrated in Example 1 (page 15) of the instant specification.

In response it is respectfully submitted that it is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

In the instant specification the data presented to demonstrate the synergistic effect of L-methadone and morphine is not commensurate with the scope of the claims. For example, while the instant claims are directed to enantiomerically pure L-methadone or a mixture of DL-methadone having at least 65% L-methadone, the data provided in Table 1 only demonstrates the effect of a combination of L-methadone with an opioid analgesic. Furthermore, while the instant claims are directed to opioid analgesics in general, the data provided in Table 1 and Figure 1A demonstrates that certain opioid analgesics do provide a synergistic effect (morphine, M6G, codeine, and 6-AcMorphine) while others do not (oxymorphone, oxycodone, fentanyl, alfentanyl, and meripidine). It is also noted that the interaction of L-methadone and the opioid is measured at a fixed dosage, and that this dosage is not indicated for all of the drugs, including L-methadone (see page 16, lines 6-21). Thus, it is unclear at what dosage the synergistic effect occurs, and if the synergistic effect occurs in a dosage commensurate with the scope of the dosages as claimed for L-methadone and the additional opioid analgesic. Therefore, no clear and convincing unexpected results are seen to be present herein.

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

REJECTIONS

5. The following rejections and/or objections are either reiterated from the Office Action dated 5/14/2008 or newly applied. They constitute the complete set of rejections

and/or objections presently being applied in the instant application. The newly applied rejections are necessitated by the amendment of claims 3-6 and 20-25.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 3-9 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. ("Analgesics. I. Effect of Analgesic Combinations on Reaction Time in Rats," *Journal of Pharmacology and Experimental Therapeutics*, 1954, 108, pgs 336-339) as applied to claims 3-4, 7-9 and 2-25 in view of Inturrisi (US 6,008,258).

The instant claims 3-9 and 20-23 are directed to methods of providing analgesia comprising administering a pharmaceutical composition(s) comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, and morphine, wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response. Claims 24-25 are directed to methods of potentiating an antinociceptive response comprising administering a pharmaceutical composition(s) comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, and morphine, wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response.

In regards to the recitation in claims 3-4 of "wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response," the amounts and duration sufficient to obtain this effect is not defined in the specification. Therefore, claims 3-4 and 22-25 (all containing similar recitations) are broadly interpreted as administering any amount of L-methadone and morphine in any manner or duration.

Smith et al. teach a method of providing analgesia to rats, whose tails are exposed to a beam of light of constant intensity, by administering a combination of methadone and morphine via subcutaneous injection (see page 336, Materials and Methods, and pages 337). The methadone taught by Smith et al. is considered to be a racemic mixture of D and L racemates, and thus comprises L-methadone. Smith et al. further teaches administering methadone in a dosage of 1 mg/kg of body weight of the rat, and morphine in 4 mg/kg of body weight of the rat as claimed in the instant claims 8-9 (see page 228, Table 2).

Smith et al. does not teach methods of providing analgesia wherein the methadone is a mixture of DL methadone having at least 65% L-methadone or enantiomerically pure L-methadone. Furthermore, while Smith et al. teaches a dosage of 1 mg of methadone, Smith et al. does not explicitly teach the dosage ranges as claimed for a mixture of DL methadone having at least 65% L-methadone or enantiomerically pure L-methadone in the instant claims 5-6.

Inturrusi teaches that the L-isomer of methadone is responsible for the opioid properties, whereas the D-isomer is weak or inactive as an opioid (see column 3, lines 21-23). In an exemplary test, Inturrusi further teaches that L-methadone produces dose-dependent antinociception (analgesia) in rats with an ED_{50} value of 15.6 μg/rat, while D-methadone produced no antinociceptive effects at doses from 20 to 460 μg/rat. (see column 3, lines 51-57).

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ either an increased amount of the active L-isomer of methadone or

pure L-methadone as taught by Inturrusi, in the racemic mixture of methadone used in the method of providing analgesia taught by Smith et al.

One of ordinary skill in the art would have been motivated to use an increase amount of L-methadone or enantiomerically pure L-methadone because the L-isomer of methadone is the active isomer of methadone in terms of providing opioid analgesia. Additionally, it would have been obvious to one of ordinary skill in the art to optimize the dosage of L-methadone or a mixture of DL methadone having at least 65% L-methadone. While the prior art references do not explicitly teach the dosage range of L-methadone, the determination of an optimal dosage of L-methadone by routine experimentation is obvious absence a showing of criticality of the dosage. One have ordinary skill in the art would have been motivated to optimize the dosage of L-methadone in order to achieve the desired analgesic effects.

In regards to claims 24-25, the ability of compositions comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone and morphine to potentiate an antinociceptive response is obviously present in the method of providing analgesia obvious over Smith et al. in view of Inturrusi et al. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979).

Conclusion

All claims have been rejected; no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617